Finding A Path To An Effective Shigellosis Vaccine

University of Maryland

In the worldwide attempt to combat disease, shigellosis may not garner considerable public attention, but its impact is devastating, particularly on the world's poorest children. Annually, the infectious disease causes some 165 million cases of severe dysentery worldwide, including more than a million deaths, according to the World Health Organization.

The group of bacteria involved, called *Shigella*, tends to inflict the most harm in developing regions with poor sanitation, as it is spread through contaminated food or water, as well as person to person. Those who don't die from the diarrhea and severe dysentery, including bloody stool, may be ill for weeks to months. Children in their first few years of life are most vulnerable both to becoming ill and the resulting long-term effects, according to Richard Walker, Ph.D., director of the Enteric Vaccine Initiative at PATH, a nonprofit international health organization. Even children who survive the infection may suffer damage to their intestinal lining and stunted growth, among other effects, says Walker.

Meanwhile, the antibiotics traditionally used to combat the microscopic organisms are becoming less effective, says Walker. "In the developing world, since they use antibiotics so frequently, a lot of pathogens have become resistant to them. *Shigella* is becoming much more resistant."

In 2007, PATH received a $50 million grant from the Bill & Melinda Gates Foundation to help develop two vaccines—one against *Shigella*, and one to combat another diarrheal illness called enterotoxigenic *Escherichia coli* (ETEC). With the funds, PATH is providing vital seed money for some of the most promising vaccine avenues.

According to Walker, ideally, one or two vaccine candidates for each disease will be identified that show sufficient promise to be pursued in Phase 3 trials, by far the most costly phase of vaccine testing. "Our job is to find good (vaccine) ideas and help move them along," he says. "And, if subsequent data warrants, get them to an organization that can actually manufacture (the vaccine) and distribute it."

Shigella Vaccine Hurdles

Shigella, first identified more than 100 years ago by a Japanese scientist named Shiga, is actually a family of bacteria. To date, more than 50 types and subtypes have been identified, falling into four species. For at least 40 years, researchers have been striving to create a live oral *Shigella* vaccine that can be safely tolerated, Walker says. Similar to other live vaccines, such as oral polio, the goal has been to incorporate a weakened—also known as attenuated—strain of the organism involved, thus inducing the body to develop a protective response.

The challenge, in terms of a *Shigella* vaccine, has been providing vaccine recipients with sufficient immunity without also exposing them to the bacteria's toxic side effects, such as diarrhea. The Center for Vaccine Development at the University of Maryland School of Medicine, led by Myron M. Levine, M.D., D.T.P.H., has made some intriguing discoveries toward resolving this challenge.

The center, founded in 1974, has been working for more than a decade to undercut the organism's toxicity while still fostering a sufficient vaccine response. The center also is relatively unique in that it contains not just research labs, but other facilities that enable it to conduct related clinical trials. So when PATH received the Gates funding, Levine's research team was one of the candidates they approached as they solicited requests for proposals.

Immunity vs. Toxicity

Safety has been an overriding concern, since young children will be any vaccine's primary target. How do you reliably disarm this organism, but don't totally disarm it so the body doesn't see it as a danger…and then the body doesn't create protective immune responses?" Levine asked. "You want to get
immunity. You want to fool the body."

Levine, a long-time researcher, and his team had several critical breakthroughs as they worked to defuse *Shigella's* toxic elements. One breakthrough occurred in the mid-1990s when the center's researchers identified two enterotoxins in *Shigella flexneri* 2a that led to the onset of watery diarrhea. Once researchers knew those enterotoxins—enterotoxin 1 and enterotoxin 2—were present, the next step was to disarm them. Using genetic engineering, they were able to knock out the genes responsible for telling the organism to make those toxins.

Then the researchers were ready to test a vaccine prototype. In the Phase 1 study, Levine's researchers divided 28 healthy adult volunteers into two groups. Each group received one of two vaccine prototypes, each of which contained

a weakened form of *Shigella flexneri* 2a. Levine describes flexneri 2a as the single most common *Shigella* culprit and maintains that inthe developing world the strain is responsible for 25 to 50 percent of all cases.

During the Phase 1 study, the first group ingested a vaccine prototype that contained the weakened strain, but with the two enterotoxins also knocked out. At the highest dose tested, none of those volunteers experienced any diarrhea and only one developed a brief low-grade fever, according to the findings, published in 2004 in *The Journal of Infectious Diseases*. Of the 14 adults who received a vaccine that still contained the enterotoxins, six developed mild diarrhea.

> *"The differences were highly, highly significant and indicated that the enterotoxins were really important," says Levine. "And if you knock them out, you get a well-tolerated vaccine strain. But one that still gives immune responses that we consider protective."*

Levine's group is not the only one that PATH is working with as they pursue several research avenues toward a *Shigella* solution. Walker states that PATH has a "high level of interest" in the vaccine prototype. "The key problem that Dr. Levine's group has overcome is they've greatly increased the safety of the product," he says.

Taking Concept to Market

In the fall of 2008, PATH signed a licensing agreement with the University of Maryland, Baltimore that included nearly $2.5 million to fund a Phase 2 trial of a vaccine prototype incorporating the *flexneri* 2a strain. Typically, the University of Maryland works with scientists to identify partners for promising research projects, said Elizabeth Hart-Wells, Ph.D., executive director of Commercial Ventures and Intellectual Property at the University of Maryland, Baltimore. "This one was definitely Dr. Levine's doing to find a partner to develop this technology," she says.

The Phase 2 trial, which will involve about 60 volunteers, is slated to launch in 2009. Levine is quick to stress that he is only part of a trio of *Shigella* researchers at the center, with Eileen Barry and Karen Kotloff performing much of the heavy lifting in running the related clinical trials and engineering the vaccine prototypes.

If the *flexneri* 2a prototype continues to look promising, the next step would be to test the vaccine on a trial basis in the developing world, starting with older adults and moving down in age, as the vaccine is assessed for relative safety and effectiveness. "The *flexneri* 2a that we are looking at right now is the dominant strain of *Shigella* that's a problem in developing countries," Walker said. "So even by itself, it could be a significant vaccine."

Long term, Levine hopes to cast a more protective net. Eventually, he wants to build a *Shigella* vaccine that contains several strains and ideally five significant strains. Levine asserts that if the fivestrain vaccine is used broadly in the developing world, it could theoretically guard against 80 to 90 percent of all *Shigella* disease, adding, "Our goal is the definitive broad-spectrum vaccine."

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